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IN BUSINESS FOR LIFE

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ELECTRONIC AND HAND DELIVERY

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Genentech, Inc. ("Genentech") submits this petition to the Food and Drug Administration ("FDA") under 21 CFR 10.30, section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 USC 355(b)(2) (hereafter, "section 505(b)(2)"), section 351 of the Public Health Service Act ("PHSA"), 42 USC 262 (hereafter, "section 351"), Section 301(j) of the FDCA, 21 USC 331(j) (hereafter "section 301(j)"), the Trade Secrets Act, 18 USC 1905, and the United States Constitution to request the Commissioner of Food and Drugs refrain from taking steps that prejudice Genentech's property rights in trade secret and confidential commercial data and information provided to the agency for the limited purpose of reviewing and approving Genentech's products.

Specifically, Genentech requests the Agency to refrain from publishing a draft guidance document setting forth standards for the "similarity" or "sameness" of biotechnology-derived products and approving an application filed under section 505(b)(2) with respect to a biotechnology-derived product that relies, directly or indirectly, on Genentech's trade secret and confidential commercial data and information. Genentech also urges the agency to establish procedures governing the review of applications filed under section 505(b)(2) that will prevent unauthorized use of or reliance upon Genentech trade secret or confidential commercial data and information by employees of the agency or by third parties. Should the FDA either publish a draft guidance or approve an application under section 505(b)(2) that relies in whole or in part on Genentech's trade secret or confidential commercial data and information before establishing procedures to safeguard that property, we request that the Commissioner provide a pre-deprivation hearing to Genentech.

We file this petition for two reasons – to protect our legal rights in our trade secret and confidential commercial data and information, and to raise

with the agency public health concerns surrounding the FDA's announced strategy toward generic biotechnology-derived products. With respect to the first point, we are concerned that any effort by the FDA to publish a draft guidance document or to approve a generic biologic product will prejudice our property interests. With respect to the second, Genentech does not believe that current science allows for reliance on analytical data and information generated from one biotechnology-derived product to support approval of a product manufactured through a different process. This belief is based on the fact that proprietary, complex operational details of the manufacturing processes themselves are central to and define the identity and unique molecular safety and effectiveness attributes of each batch of finished biotechnology-derived product. Without first examining trade secret data concerning the manufacturing processes of the innovator – something prohibited by law – agency reviewers cannot perform the rigorous scientific comparative assessment necessary to reach legitimate conclusions about the "similarity" or "sameness" of two products. Because this apparently is what the FDA is considering, Genentech is compelled to petition.

Genentech believes that credible, transparent, and rigorous scientific dialogue is essential to ensuring that the FDA implements the best policies and procedures possible to assure that biotechnology-derived products are safe and effective. The FDA must take care, however, to conduct this discussion in public and in a manner that conforms to its obligations to protect the trade secret and confidential commercial data and information entrusted to it by innovators. Because we believe that the FDA's formulation and implementation of a generic biologic policy based on a draft "similarity" guidance document and related approvals under section 505(b)(2) will necessarily rely on our trade secret and confidential commercial data and information, we request that the agency re-assess its approach. Failing that, we request that the FDA, at a minimum, put processes in place to protect our trade secret and confidential commercial data and information from use and disclosure by others – rights long established under the law and highly valued by Genentech.

This Citizen Petition uses the term "biotechnology-derived product" to refer to any therapeutic drug or biological product that is developed by biotechnology methods. It intentionally uses the term "generic biologic" to refer to a product that purports to be the same as or similar enough to an innovator's biotechnology-derived product that it may be approved for use in humans based in part on the non-clinical and clinical data developed by an innovator company for an original, or reference, product. We do not use the term "follow-on biologic" because that term has been used in the past to refer to a product that enters the market based on a full complement of data but is

not the first biotechnology-derived product approved for a particular use. This Citizen Petition also uses the phrase "manufacturing processes" to refer to the entire set of methods and controls used to produce, process, purify, and otherwise manufacture the biotechnology-derived product.

A. BACKGROUND AND ACTIONS REQUESTED

Genentech is a leading manufacturer of biotechnology-derived products. Over the past 28 years, we have invested over $6.4 billion in research and development, and have discovered and introduced over a dozen significant therapies for serious and life-threatening diseases, including cancer, heart disease, as well as pulmonary disease. Our record demonstrates that we have been in the forefront of developing innovative, safe, and effective products using cutting-edge biotechnology processes. Presently we produce the majority of the world's supply of protein-based biotechnology-derived products.

Specifically, we received approval in 1985 to market synthetic human growth hormone Protropin® (somatropin for injection), one of the first biotechnology-derived products manufactured and marketed in the United States. This was soon followed by approval of Activase® (alteplase), a human tissue-plasminogen activator (tPA) for use in dissolving blood clots in patients suffering from acute myocardial infarction. Since then, we have developed and received approval for numerous breakthrough drugs, including Pulmozyme® (dornase alpha), the first new therapy for treatment of cystic fibrosis in 30 years; Rituxan® (rituximab), for treatment of B-cell non-Hodgkin's lymphoma; Herceptin® (trastuzumab), for treatment of breast cancer; and most recently, Avastin® (bevacizumab), a breakthrough oncology product discovered by Genentech scientists that functions by the unique biologic mechanism of starving tumors of the blood supply needed to thrive and grow, and proven safe and effective in the treatment of colorectal cancer.

Each innovative therapy required Genentech to undertake significant commercial risks, and to expend a substantial investment of time, resources, energy, and overall know-how in scientific discovery, development, and clinical testing. In the course of translating these developments into therapeutic medical interventions, we have generated valuable trade secret and confidential commercial data and information about each product and how it is manufactured. And, each time we seek marketing approval for a new product or grant FDA investigators access to manufacturing facilities, we provide commercially sensitive and valuable information to the FDA for the specific and limited purpose of allowing the agency to review the safety and effectiveness of the product under review.

Although Genentech relies extensively on its patents to protect inventions arising from research activities, and publishes extensively in the scientific literature, we also rely heavily on trade secret protection provided by State and Federal law to protect our confidential information and know-how. We carefully safeguard trade secrets by implementing a range of precautions from special handling procedures for information to physical security restrictions for facilities where trade secrets are in use. We even limit our own employees' access to confidential information. The purpose is clear – our trade secrets are valuable corporate assets, and we take appropriate measures to effectively protect those assets. Consequently, Genentech has a direct interest in how the FDA intends to handle and use such information, especially in light of statements concerning the agency's plans to publish a draft guidance document setting out a scientific framework for review and potential approval of generic biologic products and in light of its approach to reviewing applications filed under section 505(b)(2).

Foremost in any discussion about generic biologics must be the legal principles establishing and protecting the trade secret and confidential commercial data and information contained in and integral to Genentech's applications submitted to the FDA. For decades, the FDA has rightly taken the position, based on solid scientific evidence, that each biotechnology-derived product is a unique product inexorably linked to and inseparable from the manufacturing processes used in its creation. And, through regulations and administrative practices, the agency has protected the trade secrets and confidential commercial data and information that Genentech has provided concerning biotechnology-derived products, including extremely sensitive manufacturing know-how and related information. These principles and practices have established the regulatory and legal foundation on which Genentech has submitted its marketing applications to the FDA for its review.

It is apparent, however, that the FDA is backing away from this long-standing position. Two events, in particular, raise concerns. First, agency officials have publicly acknowledged that the FDA is drafting a guidance document that establishes a framework for how a generic manufacturer might show that its product is "similar" enough to a pioneer product, allowing the generic to rely on the innovator's safety and effectiveness data. Genentech does not believe that the FDA can develop and publish such draft guidance without relying upon and using the trade secret and confidential commercial data and information provided to the agency by innovators. The FDA has gained a tremendous amount of knowledge about biotechnology-derived products and the way they perform in the human body through reviewing the trade secret and confidential commercial data and information of companies like Genentech. The "knowledge base" on which the FDA will rely in drafting

the proposed guidance therefore consists of a significant amount of information obtained from innovators that was provided to the agency both confidentially and for the explicitly limited purpose of enabling the agency to review a particular product or facility.

Second, recent events suggest that the FDA currently does not have an administrative process designed to prevent the unauthorized use or reliance on trade secret and confidential commercial data and information when reviewing applications submitted by non-innovators. For example, on February 4, 2004, the agency issued an Administrative Stay of Action with respect to new drug application ("NDA") 21-435 for amlodipine maleate from Dr. Reddy's Laboratories. *See* Exhibit 1, attached. Dr. Reddy's seeks approval under section 505(b)(2) of a different salt form of amlodipine than that marketed by Pfizer, Inc., and the FDA approved Dr. Reddy's drug based on "findings" that Pfizer's amlodipine besylate was safe and effective.1/ But, the FDA stayed the Dr. Reddy's approval because "questions [were] raised about the source of data the [FDA] relied on in approving" the NDA. *Id.* Although the agency has said no more about its grounds for staying the approval, Genentech is concerned that FDA reviewers inappropriately relied on Pfizer's NDA data. *Id.* We are concerned that such improper reliance could occur again under section 505(b)(2) unless the FDA acts to clarify for agency review staff that an innovator's trade secret manufacturing data – data essential to the review of any biotechnology-derived product – may not be used in the course of evaluating a competitor's application. We are similarly concerned about the protection of our confidential commercial information.

Genentech does not contest application of the FDA's traditional approach to "paper NDAs" under section 505(b)(2), under which approvals may be based on clinical and other data and information appearing in publications or through use of processes Genentech invented but later published through patent applications or otherwise.2/ The traditional approach to section

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1/ *See* October 14, 2003 letter from J. Woodcock, FDA, to Ms. Sanzo and Messrs. Chasnow, Lawton, and Rakoczy, regarding FDA Dockets No. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1 ("Petition Response"). These "findings" are a new construct for the FDA. There is no "findings" section in a drug's approved labeling or in agency pre-approval reviews. The FDA has not defined the parameters of "findings," when the agency will make them, whether the agency will publish them, or how the innovator company (whose data is being used to make them) will learn of the findings and, if necessary, protest any that it believes are unwarranted based on its data.

2/ Over the years, Genentech has balanced its interests in protecting its know-how and trade secrets with the public benefits of patent protection and has chosen to patent certain manufacturing processes. *See generally, Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 485

505(b)(2) applications, however, requires any such applicant to draw from the public literature a complete package of information that is sufficient, standing alone, to support a reasoned decision by the agency to approve the drug product. We draw the line, however, at agency reference to or reliance on Genentech trade secret and confidential commercial data and information to approve a competitor's product.

As we will show, Genentech does not believe that the agency can draft a guidance document or safely approve a biotechnology-derived product based on "findings" about a Genentech product without relying – directly or indirectly – on trade secret and confidential commercial data and information that we provided to the FDA for an explicitly limited purpose, *i.e.*, review of Genentech products and the specific processes used to make them. Unlike small-molecule drugs, which are generally produced by chemical synthesis, biotechnology-derived products are complex proteins that cannot be adequately compared scientifically based solely on analytical methods. In other words, because the manufacturing processes dictate the product attributes, a scientifically valid comparison cannot be established without reference to and detailed information about the manufacturing processes used to create them. Because making such reference and using such information would violate longstanding agency policy, State and Federal statutes, and the United States Constitution, the agency should refrain from acting further until it puts in place a mechanism through which the protection of Genentech's proprietary information and our legal rights can be assured.

Therefore, Genentech requests that the Commissioner of Food and Drugs:

- refrain from issuing a draft guidance document describing the principles of determining the "similarity" or "sameness" of protein based biotechnology-derived products, and
- refrain from approving a biotechnology-derived product characterized as "similar" to or the "same" as a Genentech product based on agency "findings" of safety or effectiveness for a Genentech product that relies in whole or in part on the trade secret and confidential commercial data and information of Genentech, and
- develop a process under which Genentech will receive notice of any potential use of its trade secret or confidential commercial data and

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(1974). Therefore, once our patent protection expires, we have no objection to a competitor using that information to replicate or reference Genentech processes and controls.

information and may intervene to stop such use or disclosure before it occurs.

B. STATEMENT OF GROUNDS

1. COMPLEX BIOTECHNOLOGY PROCESSES ARE TRADE SECRETS THAT THE FDA MAY NOT USE TO DEVELOP A GUIDANCE DOCUMENT

a. The Biotechnology Manufacturing Process

Biotechnology is "the application of biological systems and organisms to technical and industrial processes."3/ Genentech's biotechnology-derived products are proteins that constitute biological or drug products and are produced using a series of processes we have developed. Because our biotechnology-derived products are made from living organisms, a trivial change to the manufacturing processes or respective controls used to make a particular product can have significant consequences on the compositional or conformational makeup – hence on the safety and effectiveness – 4/ of that product.5/ Therefore, knowledge of the manufacturing processes used to make a particular biotechnology-derived product is "an integral component in determining" how to assess the impact of manufacturing differences on that product, as well as assessing its safety and effectiveness.6/

Biotechnology-derived products are produced through complex manufacturing processes. A host cell is genetically engineered to produce a particular protein which that cell does not normally make and which is sought for its therapeutic value. Once Genentech scientists choose a particular cell that can produce the desired protein quickly and at high yield levels, we create a master cell bank from which the desired protein can be produced and purified. Cells from the master cell bank are used initially to create a seed stock that then is grown through a fermentation process to create a large

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3/ FDA Biotechnology Inspection Guide Reference Materials and Training Aids (Nov. 1991).

4/ . In this Petition, Genentech uses the term "safety and effectiveness" to encompass clinical data used to establish the safety, purity, and potency of products regulated under the PHSA. *See* 21 CFR 600.3(p), (r), (s).

5/ *See* FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products (April 1996) ("April 1996 Comparability Guidance").

6/ *Id.* at 6. *See also,* FDA Draft Guidance for Industry: Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing, and Controls Information, at 6 (Sept. 2003).

amount of the desired protein. *See* Gary Walsh, Biopharmaceuticals: Biochemistry and Biotechnology, at 127-28 (2d ed. 2003). All of the factors surrounding fermentation are critical to the growth of the cells and the protein's biological activity. The process requires careful design of and a specifically tailored culture medium to obtain a protein product both in high yield and having a particular, desired structural characteristics.

The fermentation process generates impurities that must be removed from the bulk solution during the purification process. Many of these impurities are the normal by-products of the living cells that are used to produce the therapeutic product. Several different steps may be used to purify a bulk – steps which (both with respect to type and sequence) are critical to the biological activity of the bulk substance. *Id.* at 134-40. These steps are considered "highly confidential by the manufacturer" and are therefore "rarely made generally available." *Id.* at 134-36. Importantly, Genentech applies its technical know-how and carefully designs each step to remove particular impurities created from the fermentation processes we use. *See id.* at 142-43. Then, we apply analytical tests (in many instances, specifically tailored to the process, including the application of uniquely developed reagents) to determine whether the protein product has the desired structure and biologic properties and whether the known impurities are removed or reduced to a level where they will not have adverse consequences in humans.

After a bulk substance is isolated and purified, it is formulated into a finished biotechnology-derived product that is either lyophilized or filled into vials for administration to patients. *See id.* at 153-58. Throughout this process, we monitor and evaluate the properties of the protein and the finished biotechnology-derived product. These controls pertain to both the protein's production and to the detection of agents and/or derivatives that may affect the activity or safety of the ultimate biotechnology-derived product. Because the manufacturing processes and respective controls, in total, invariably influence the physical and biological properties of the protein molecule, the therapeutic properties of the molecule – encompassing both safety and effectiveness – cannot be assessed in the abstract.

The processes we employ produce therapeutic products that are completely and fundamentally different from small-molecule chemical drugs. Small-molecule drugs are not made in living cells but rather are made using a repetitive, reproducible assembly line-like processes of chemical synthesis. Small-molecule drugs are also different from biotechnology-derived products in that they can easily be identified through basic techniques of analytical chemistry. For example, small-molecule drugs can be subjected to purification and crystallization, which allow for full chemical characterization, and to

sterilization techniques that would denature a protein "product." Similarly, small-molecule drugs can be subjected to analytical procedures that identify impurities or variants that might affect the activity of a biological product.

Moreover, unlike the situation with a small-molecule drug, subtle changes to a biotechnology-derived product that may impact its safety and effectiveness are not always apparent. Unless two biotechnology-derived products are produced by an identical process, analytical testing alone is insufficient to determine whether they are the same. This inevitable inseparability of product and process has been validated repeatedly. The only circumstances in which the utility of product comparability using analytical methods has been demonstrated are where a manufacturer makes a minor and very controlled change to its own well-developed and understood manufacturing processes. Therefore, the therapeutic properties of the molecule cannot be assessed without access to information about the manufacturing processes used to create the molecule.

Of course, the FDA has access to the full array of our manufacturing information – both for products in development and products approved for marketing. The FDA gains this access through applications we submit to the agency for review and approval. In those instances we grant a limited license to the FDA to review detailed trade secret and confidential commercial data and information so that the agency may reach a determination that our proposed product is safe and effective. Additionally, the FDA also enjoys complete access to our manufacturing facilities during inspections – access that no other person or entity enjoys. During inspections, FDA investigators may review highly guarded trade secret and confidential commercial data and information concerning, among other things, the "formulas" used to produce our fermentation media and the specific purification steps in use on our biological production lines.7/ Therefore, it is critical that the agency take appropriate steps to safeguard this valuable information.

b. Information and Data About Biotechnology Manufacturing Processes Are Trade Secrets

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7/ After years of these inspections, Genentech has observed that FDA standards for current good manufacturing practice ("cGMP") have become increasingly rigorous. As a general rule, agency investigators demand that Genentech demonstrate strict adherence to concepts of "reproducibility" primarily through repetitive manufacturing steps. This cGMP policy seems directly at odds with a generic biologic approval policy where a generic manufacturer would never be able to reproduce Genentech's manufacturing processes unless it had access to our trade secret and confidential commercial data and information, and was able to replicate the manufacturing processes to the same exacting standards that Genentech is held to.

A "trade secret" is "[a]ny formula, pattern, device or compilation of information which is used in one's business, and which gives him an opportunity to obtain advantage over competitors who do not know or use it. It may be a formula for a chemical compound, a process of manufacturing, treating or preserving materials, a pattern for a machine or other device, or a list of customers. . . . A trade secret is a process or device for continuous use in the operation of the business." Restatement of Torts, Sec. 757, cmt. b (1939). *See also Ruckelshaus v. Monsanto Co.*, 467 U.S. 986 (1984) (applying the Restatement definition).

Trade secret law is a creature of State law and is not displaced or preempted by Federal law. *Kewanee Oil,* 416 U.S. at 474-75. Thus, Genentech's trade secrets – which arise under California law – are protected property interests. *See* Cal. Civ. Code § 3426.1(d) (trade secret means "information, including a formula, pattern, compilation, program, device, method, technique, or process that: (1) Derives independent economic value, actual or potential, from not being generally known to the public or to other persons who can obtain economic value from its disclosure or use; and (2) Is the subject of efforts that are reasonable under the circumstances to maintain its secrecy"); *see also Whyte v. Schlage Lock Co.*, 101 Cal. App. 4th 1443, 1456 (Cal. Ct. App. 2002) (process technologies and technological "know-how" is the "quintessential trade secret" in California).

Public policy concerns do not trump trade secret protections. *Philip Morris, Inc. v. Reilly*, 312 F.3d 24, 44 (1st Cir. 2002) (State statute aimed at protecting public health through ingredient labeling of tobacco products was facially unconstitutional). In fact, effective trade secret protection standards strongly support public policies that yield significant, continuing benefits for public health. As noted above, many of the trade secrets held by Genentech concern process technologies we have created during development of our new products. Although certain of these technologies might qualify for patent protection, many others have a very narrow but significant commercial application, or present particular hurdles that discourage our seeking patent protection. Regardless, these trade secret procedures and know-how enable us to assure, and the FDA and the public to rely on, the safety and effectiveness of our products.

As the Supreme Court noted more than thirty years ago:

> Trade secret law encourages the development and exploitation of those items of lesser or different invention than might be accorded protection under the patent laws, but which items still have an important part to play in the

> technological and scientific advancement of the Nation. Trade secret law *promotes the sharing of knowledge*, and the efficient operation of industry; it permits the individual inventor to reap the rewards of his labor by contracting with a company large enough to develop and exploit it.

Kewanee Oil, 416 U.S. at 493 (emphasis added). Thus, trade secret protection not only promotes innovation, it also performs a function integrally linked to the FDA's accepted role in ensuring the safety and effectiveness of approved products.

The FDA has historically been very careful to respect the trade secret status of innovators' data and information concerning proposed and approved biotechnology-derived products. The FDA likewise respects the trade secret status of data and information it gains through authorized inspections of manufacturing facilities. And, FDA regulations are consistent with well-established trade secret standards *See* 21 CFR 20.61(a) (protecting any "commercially valuable plan, formula, process, or device" used to make, prepare, compound, or process commodities that are the end product of innovation or substantial effort). All the information included in the chemistry, manufacturing, and controls ("CMC") portion of an NDA or in the parallel provisions of a biological license application ("BLA") fall within the FDA's definition of a trade secret. *Public Citizen v. FDA*, 997 F. Supp. 56, 61 n.2 (D.D.C. 1998) (CMC data is trade secret), *reversed and remanded on other grounds,* 185 F.3d 898 (D.C. Cir. 1999); *Bowen v. FDA*, 925 F.2d 1225, 1227-28 (9th Cir. 1991) (trade secrets include "manufacturing formulas and processes, as well as quality control and internal security measures"); *Heeney v. FDA*, 2001 WL 371921, at *1 (slip copy) (9th Cir. 2001) (affirming decision that "product design, testing, and manufacturing data, construction materials" are trade secrets). *See also* section 520(h)(4) of the FDCA, 21 USC 360j(h)(4) (hereafter "section 520(h)(4)") (excluding from use or disclosure "descriptions of methods of manufacture and product composition and other trade secrets for medical devices").

As do our competitors, Genentech carefully guards trade secret data and general "know-how," as well as other valuable information about our products, like clinical trial data. Specific information about the steps, equipment, organisms, and production and purification variables used to produce our products is closely protected and kept secret. We require employees to sign non-disclosure agreements and all outside consultants and other companies and individuals with whom we do business or discuss confidential information to sign confidentiality agreements. We limit access to our manufacturing facilities, to our computer systems, and to records and reports related to

formulas, methods and processes of production, quality control tests, and other relevant materials to those who have need to access them. We employ physical barriers such as controlled doors, security cameras, and area-specific electronic card-keys to limit access to our facilities to those individuals whose activities necessitate such access. We employ a security staff to assure that those on our premises are either employees or guests, and all guests are required to register upon arrival. As the value of the information at issue increases, access to that information within Genentech's ranks decreases substantially.

In these circumstances, each step in the manufacturing process, as well as the process *in toto*, is considered a trade secret under State law. *See Components for Research, Inc. v. Isolation Products, Inc.*, 241 Cal. App. 2d 726, 728-29 (Cal. Ct. App. 1966); *see also Wyeth v. Natural Biologics, Inc.*, 2003 WL 22282371, at *19 (D. Minn. 2003). Thus unless information about the cell line, manufacturing, purification, and other steps related to the production of one of our biotechnology-derived products is placed in the public domain through patent disclosure or a scientific publication, the information is a protected trade secret.

c. The FDA Cannot Use or Disclose Trade Secret Data

Federal law expressly prohibits the FDA from either using or disclosing Genentech's trade secrets. The FDCA prohibits:

> the using by any person to his own advantage, or revealing, other than to [other members of the Department of Health and Human Services], or to the courts when relevant in any judicial proceeding under this chapter, any information acquired under authority of [various FDCA sections] concerning any method or process which as a trade secret is entitled to protection.

Section 301(j). Congress included section 301(j) to "safeguard the property rights of the manufacturer,"8/ and the FDA interprets the statutory phrase "to his own advantage" to encompass the use of one manufacturers' protected

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8/ S. Rep. No. 74-361, at 27 (1935); *see also* S. Rep. No. 73-493, at 18, 21 (1934). Congress has also authorized the FDA to release trade secrets to agency contractors, but the contractors must take precautions to secure the data and information. Section 708 of the FDCA, 21 USC 379. Even where Congress has permitted the agency to release safety and effectiveness data or to use it to establish the safety and effectiveness of another product, it has excluded trade secret data from such disclosure or use. Section 520(h)(4).

information for the benefit of another person. Recognizing that trade secrets are "entitled to significant and heightened protection under Federal law," the FDA requires State and local officials to certify, prior to acceptance of an FDA commission, that they will not use trade secrets to further a private financial interest or the financial interests of another person. Regulatory Procedure Manual ("RPM"), Ch. 3, Commissioning State and Local Officials; Exhibit 3-7 thereto, *Acceptance of Commission.* The FDA has always applied these policies broadly to cover biological products.9/ This trade secret status is absolute and does not change over time.

The Freedom of Information Act ("FOIA"), 5 USC 552(a), similarly does not permit the FDA to disclose the trade secrets in its possession to the public or to another company. The FOIA's disclosure provision "does not apply to matters that are -- . . . (4) trade secrets." *Id.* at 552(b)(4). In the absence of a statute mandating disclosure, the only way an agency can properly disclose trade secret materials under the FOIA is through the issuance of a duly promulgated regulation. *Chrysler Corp. v. Brown*, 441 U.S. 281, 301-02 (1979). Making such a disclosure without authorization is both inconsistent with the FOIA and violates the Trade Secrets Act. 18 USC 1905; *e.g., McDonnell Douglas Corp. v. NASA*, 180 F.3d 303, 305 (D.C. Cir. 1999) (quoting *CNA Fin. Corp. v. Donovan,* 830 F.2d 1132, 1151 (D.C. Cir. 1987)) (scope of the Trade Secrets Act is "at least coextensive with that of Exemption 4 of [the FOIA, 5 USC 552(b)(4)]").

Consequently, legal protections afforded to trade secrets provided to the FDA prohibit the use or disclosure by the FDA of Genentech's trade secret information. The protection from unauthorized use of trade secrets conferred by Federal statutes extends to any use that would erode or eliminate the commercial value of the trade secret. In this respect, the use by FDA employees of trade secret information – for example by fashioning an approval pathway that draws upon Genentech know-how not found in the public domain – would not constitute an authorized "use" of our trade secrets.

Despite the longstanding FDA policy on trade secret protection, senior FDA officials have stated that the agency is developing a draft guidance document based on "everything the agency knows" about biotechnology-derived products. *See, e.g.,* Center for Drug Evaluation and Research, *Dr. Woodcock Provides Highlights of her Detail*, News Along the Pike, at 8. (Jan.-Feb. 2004),

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9/ *See* August 20, 1996 letter from V. Zonana, HHS, to R. Theis at 3 (hereafter "August 1996 Zonana letter") (relying on section 301(j) to deny release of "manufacturing methods or processes, production data, comparability data, and safety and effectiveness data" contained in a BLA), attached at Exhibit 2.

attached as Exhibit 3. The proposed guidance will set out how a generic manufacturer might show that its product is "similar" enough to a pioneer product approved under an NDA or BLA to allow the generic manufacturer to rely on the innovator's safety and effectiveness data. *See id.* Genentech is extremely concerned, however, that any such draft guidance document will improperly rely on our protected trade secret data for the simple reason that the FDA has gained essentially all of its knowledge about the safety and effectiveness of our biotechnology-derived products through review of trade secret and confidential commercial data and information in our marketing applications – applications that remain the protected property of Genentech.

d. The FDA Cannot Use Genentech's Trade Secret Data To Publish a Draft Guidance Document

FDA officials have further acknowledged that the proposed draft guidance will be based on the innovator biotechnology industry's experience with comparability assessments.10/ Under the comparability policy, the FDA allows biologics manufacturers in certain circumstances to institute manufacturing changes to approved processes and to support those changes with "comparability" data rather than full clinical data.11/ As a result, for example, Genentech conducted analytical and other pharmacokinetic studies on two versions of Raptiva® (one made before and another made after changes at manufacturing facilities), compared the results, and then determined in consultation with the FDA to conduct clinical trials on the product manufactured after the change.12/ The agency has gathered similar data for dozens, if not hundreds, of proposed manufacturing changes and, undoubtedly, has learned a substantial amount about the usefulness of comparability data as well as the ability of manufacturers to safely initiate process changes.

This know-how and data, however, cannot be used by the agency to draft a guidance document concerning the potential "similarity" of a Genentech product to another manufacturer's product. Because they concern manufacturing changes, all comparability study results are submitted to and

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10/ During a January 29, 2004 meeting between representatives of the Biotechnology Industry Organization and FDA staff, agency officials stated that the agency would use manufacturers' comparability data to create the draft guidance.

11/ *See* April 1996 Comparability Guidance.

12/ *See* Brady Huggett, *Genentech, Xoma Come Through With Strong Phase III Raptiva Data*, 13 BIOWORLD TODAY (Sept. 18, 2002); Arlene Weintraub, *Genentech's Medicine Man*, BUSINESS WEEK, Oct. 6, 2003, at 74.

reside in the CMC section of an application.13/ And, all data contained in a CMC section are trade secrets, *Public Citizen v. FDA*, 997 F. Supp. at 61 n.2, and subject to the highest protections. *McDonnell Douglas Corp.*, 180 F.3d at 305. Thus, it cannot be used by FDA employees for any purpose other than that for which it was submitted – to review a Genentech manufacturing change – and certainly not for the benefit of our potential competitors.

Moreover, agency employees cannot rely on general scientific knowledge derived from their review of our applications or a specific memory of our applications when writing the draft guidance. The fact that the source of the information is Genentech's protected trade secrets is sufficient to bar its use. This principle is well-established in the law of misappropriation of trade secrets. When employees gather valuable corporate information during their employment, the employer may lawfully limit the individual's ability to take that knowledge elsewhere. Under the doctrine of "inevitable disclosure," courts presume that even an employee acting in good faith cannot help but use or disclose the trade secrets he or she learned with a prior employer upon assuming a similar role or working on a similar project with a new employer. *See PepsiCo Inc. v. Redmond*, 54 F.3d 1262, 1269 (7th Cir. 1995).

Before the FDA initiates any policy under which "similarity" or "sameness" determinations will be made or described, it must put in place internal controls over the use of trade secret information by FDA staff in the drafting and publication of any draft guidance document. Without these initial steps, the FDA will risk violating the law and upsetting the trust it has created over decades of working with innovators.

2. THE FDA CANNOT USE GENENTECH'S TRADE SECRET INFORMATION TO PERMIT GENERIC COMPANIES TO SHORTEN THEIR DEVELOPMENT PROGRAMS

The FDA has stated that the characteristics of a finished biotechnology-derived product are inexorably linked to the manufacturing processes used to create the biologically active protein molecule. 39 FR 44602, 44641 (Dec. 24, 1974); *see also Berlex Laboratories, v. FDA*, Civil Action 96-0971-JR, Memorandum in Support of Defendant's Motion to Dismiss, at 6 (D.D.C. 1996), attached as Exhibit 4. Regardless, agency officials are now considering the scientific feasibility of allowing a generic manufacturer to perform analytical testing on its finished biotechnology-derived product in order to demonstrate

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13/ The FDA lists the April 1996 Comparability Guidance on its web page of available guidance documents under the heading, "Chemistry." *See* http://www.fda.gov/cder/guidance/index.htm.

that the product is "similar" to an approved product. Once the FDA agrees that the molecules are sufficiently similar, the generic manufacturer presumably could reference preclinical and clinical data and information derived from studies performed only on the innovator product by the innovator company. Indeed, it has been publicly acknowledged that the agency is currently reviewing a human growth hormone product under these principles through section 505(b)(2).14/ This approach, however, suffers from fundamental flaws.

a. The FDA Cannot Make Scientifically Valid Comparisons of Two Biotechnology-Derived Products Without Assessing Information About Their Respective Manufacturing Processes

Genentech does not believe that a valid comparison between two molecules – one from Genentech and one from a generic manufacturer – can be made without the FDA first consulting Genentech's know-how and trade secrets. As a fundamental matter, it is difficult to rely solely on either in-process or end-product testing when reaching conclusions about how a particular biotechnology-derived product will behave in the human body. *See* April 1996 Comparability Guidance. As a practical matter, before assessing the results of a particular analytical test, and even before deciding which tests are relevant and appropriate, a scientist must first examine specific information about the processes used to produce a particular molecule. Only then can the reviewer determine which analytical tests must be performed to assess the biochemical attributes of the molecule.15/ The test results at issue are meaningless without detailed information about the processes used to produce both the original molecule and the generic copy.

For example, product purity (composition) is an important factor which can influence the immunogenicity of recombinant human proteins. K. E. Stein, *Immunogenicity: Concepts, Issues, Concerns*, Biologics 2000 – Comparability of Biotechnology Products, Dev. Biol. Basel, Karger, 2002, vol. 109, 15-23 (hereafter "Stein"). Impurities can result from sources external to the product itself, such as the media, host cell proteins, or the columns used in purification, or they can result from the product itself, such as fragments or

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14/ *See* Anna Wilde Mathews & David P. Hamilton, *FDA Takes Step Toward Allowing Generic Versions of Biotech Drugs*, WALL. ST. J., Feb. 18, 2004, at A1.

15/ *See* M. Field et al., *The Use of High-Performance Anion-Exchange Chromatography and Matrix-Assisted Laser Desorption/Ionization Time-of Flight Mass Spectrometry to Monitor and Identify Oligosaccharide Degradation*, ANALYTICAL BIOCHEMISTRY 239, 92-98, (1996) at 97 (hereafter "Field, et al.").

aggregates of the protein or chemical modifications of the product, such as oxidized forms of the molecule. *Id.*; *see also,* M.M. Federici (Jamrogowicz) et al., *Detection and Consequences of Recombinant Protein Isoforms: Implications for Biological Potency,* Dev. Biol. Basel, Karger, 2002, vol. 109, 127-33 ("Some isoforms may be generated as a consequence of the manufacturing process. Bioassay methods may not be sufficiently sensitive enough or specific enough to determine the biological effect of having a new or increased level of a particular isoform.") Because all of these product-related or process-related impurities can lead to immunogenicity or other untoward events in patients, very specific and sensitive assays must be developed to test the purified bulk substance throughout the manufacturing processes. Often, testing is performed using product-specific assays, which make direct comparisons across products "inappropriate," especially when the products are produced by different processes. *Stein,* at 16-17. Dr. Stein advises, "comparisons across products should not be made." *Id.* at 17.

Therefore, before performing a scientifically valid comparison of analytical test results about different biotechnology-derived products, the FDA would need to consult detailed information about Genentech's product – including the trade secret processes used in its manufacture as well as confidential commercial preclinical and clinical data. This consultation could take several forms – all equally improper. The FDA official could consult agency review or inspection files that contain Genentech's trade secret and confidential commercial data and information or could rely on memory of that information from a previous application review or inspection. All constitute unauthorized uses of Genentech's trade secret information.

b. The Manufacturing Process is Central to the FDA's Safety and Effectiveness Determination for Biotechnology-Derived Products

Long-standing FDA policies reflect the agency's appreciation that even minor manufacturing changes can result in changes to the molecule that are difficult to detect and that can have significant effects in patients. As the FDA states:

> Manufacturing changes may result in no observed alteration in a product. Alternatively, a minor alteration in one or more product characteristics, with no previously documented effect, can have either no effect or a substantial effect on the pharmacology of the product. Likewise, a major alteration in one or more product characteristics with no documented effects on the pharmacology of

> the product, can have either no effect or a substantial effect on the pharmacology of the product.

April 1996 Comparability Guidance. Thus, companies must often perform clinical tests after instituting manufacturing changes to be assured that the product produced after the change can be safely and effectively used in patients. *Id.* The FDA imposes these requirements to gain assurance that patients are not exposed to products with unknown qualities or effects. *See* 21 CFR 601.12(e).

The importance of this type of testing is clear when one examines circumstances surrounding specific marketed biotechnology-derived products. As mentioned, Genentech began manufacturing Raptiva® at a facility different from the one in which it was originally developed, and the transition from small-scale to large-scale production required slight modifications in some steps. Analytical tests on the finished biotechnology-derived product revealed slight differences in the molecular structure which, when administered under test conditions in humans, resulted in differences in its pharmacokinetic properties.16/ Thus, Genentech performed clinical studies to compare the safety and effectiveness of the prototype to the product developed after the move to a new manufacturing facility. In this instance, there were no clinical differences in the final form of the product.

However, this example stands in sharp contrast to another well-known circumstance in which slightly modified manufacturing processes produced different clinical effects. In 2002, Johnson & Johnson ("J&J") instituted a change to its erythropoetin manufacturing processes to eliminate the use of human serum albumin due to concern about the potential transmission of Creutzfeldt-Jakob disease (CJD), a disease similar to "mad cow" disease in cattle.17/ The product resulting from the changed process did not exhibit any differences from J&J's original product. Regardless, within a few months of introducing the product in humans, some patients developed pure red cell aplasia – a severe immunologic response that results in life-long dependence on blood transfusions.18/ In essence, these patients' bodies now reject both

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16/ *See supra*, note 12.

17/ *See J & J Eprex Stability Improvements Planned in Response to Aplasia Incident*, 64 THE PINK SHEET, Sept. 16, 2002, at 24.

18/ *See* John Tagliabue, *Mystery Effect in Biotech Drug Puts its Maker on Defensive*, N.Y. TIMES, Oct. 2, 2002, at C1; Nicole Casadevall et al., *Pure Red-Cell Aplasia and Antierythropoietin Antibodies in Patients Treated with Recombinant Erythropoietin*, 346 NEW ENG. J. MED., Feb. 14, 2002, at 469-75.

recombinate erythropoetin as well as the patients' natural erythropoetin – a protein essential to the development of red blood cells.

The FDA must act carefully and only in a manner that protects patients from both an increase in the safety risk and a decrease in the potential for effectiveness. Because the scientific controls in place at two major biotechnology companies could not have predicted these therapeutic outcomes, Genentech is concerned that the path the FDA has suggested could harm patients and, consequently, the industry and the agency. *See Berkovitz v. United States*, 486 U.S. 531 (1988). Moreover, as discussed below, the pathway that the FDA has suggested could – without agency action – endanger Genentech's ability to protect its own interests.

c. The FDA Cannot Rely on Information about Our Manufacturing Processes to Compare a Competitor's Product to One of Our Products And Approve It

The agency currently anticipates performing a "similarity" analysis on two biotechnology-derived products in order to determine whether it can approve the generic version based on preclinical and clinical data and information derived from the innovator product. This will require several steps that are both scientifically and legally unsound.

As an initial matter, any potential generic manufacturer will have to isolate the therapeutic substance from Genentech's product in order to assess the physical properties of our active moiety before comparing it to the active substances created through its processes. Yet, this isolation process itself constitutes a manufacturing process that can change the characteristics of the therapeutic protein.19/ Therefore, the generic manufacturer will be comparing its molecule to one that is likely to be different from Genentech's actual substance.

Even if a generic company could compare its product to the original Genentech product, analytical testing alone, applied without detailed knowledge or information about Genentech's manufacturing processes, does not constitute a scientifically valid comparison between two products sufficient to allow preclinical and clinical data about one product to be applied to another

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19 / *See United States v. Baxter Healthcare Corp.*, 901 F.2d 1401 (7th Cir. 1990) (manufacturing steps like reconstitution and packaging taken after a drug product is approved create an unapproved new drug); D. Overcashier et al., *Lyophilization of Protein Formulations in Vials: Investigation of the Relationship between Resistance to Vapor Flow during Primary Drying and Small-Scale Product Collapse*, 88 J. PHARM. SCI., at 688-695 (July 1999).

product. For example, if hypothetical Genentech Product A were manufactured using a process resulting in the presence of residual β-galactosidase, which in turn co-purified with the desired protein, the manufacturer would have to develop certain analytical tests to detect that substance and certain purification methods to prevent it from degrading the desired protein. Field, et al., at 97. But, if hypothetical Product B contained the same desired protein manufactured from a different process that produced a neuraminidase or a protease rather than β-galactosidase as a process-related impurity, the manufacturer would need to develop a different analytical test to assess whether its purification process successfully removed that enzyme. The FDA would not be able to validly compare the results of manufacturer B's analytical tests to those from Genentech without first knowing that the processes resulted in different impurities – information that often represents proprietary Genentech know-how and constitutes a trade secret.

d. Neither the FDCA nor the PHSA Permits the FDA to Use Trade Secret Data When Approving a Generic Copy of a Genentech Product

The FDA has authority to review and approve biotechnology-derived products through the PHSA and the FDCA. The agency has established exacting regulatory requirements governing the amount and type of data and information that must be included in any BLA under the PHSA or NDA under the FDCA. 21 CFR 601.2; 21 CFR 314.50. Only in very limited circumstances may the FDA rely on clinical safety and effectiveness data (but not trade secret data) about one drug product to approve another drug product through an abbreviated new drug application ("ANDA").20/ Section 505(j)(2)(A) of the FDCA, 21 USC 355(j)(2)(A) (hereafter "section 505(j)(2)(A)"). The agency has never used this authority to approve a biotechnology-derived product produced from complex recombinant processes.21/

Recently, the agency has implemented its new policy of approving a modified small-molecule generic drug based on its previous "findings" of safety and effectiveness with respect to an innovator's reference product. *See*

20/ This reliance is grounded on the principles of "sameness." If a generic drug is an exact copy of the reference listed drug – with an identical active ingredient, dosage form, route of administration, strength, and labeling – and is bioequivalent, one can presume that the two will perform the same way in the human body. This presumption depends, however, on having a discrete drug substance of known and easily reproducible characteristics.

21/ Although the agency has approved generic copies of desmopressin under section 505(j), it is a peptide product chemically synthesized *in vitro*, *i.e.*, not in a living system such as a recombinant host cell, and is not a biotechnology-derived product.

generally Petition Response. Under the FDA's legal interpretation, the agency may rely on its "findings" that a reference listed drug is safe and effective to approve a "modified" version of a generic drug under the FDCA. The innovator's safety and effectiveness data satisfies the requirement that applications contain reports of clinical investigations set out in section 505(b)(1)(A) of the FDCA. *Id.* However, like ANDAs, section 505(b)(2) applications must still contain original CMC information required under sections 505(b)(1)(B) (components of the drug), (C) (composition of the drug), and (D) (methods, facilities and controls used in the manufacture, processing and packing of the drug). This statutory structure bars agency reference of an innovator's trade secret CMC data during review of a "modified" generic under section 505(b)(2).

When small molecule drugs are under review, there is no need for such reference or reliance. Because small-molecule drugs contain a fairly simple structure that can be determined through application of basic principles of analytical and physical chemistry, a generic manufacturer can copy a small-molecule drug fairly easily.22/ More significantly, these drugs can be analyzed through straightforward chemical tests, permitting the FDA to make a determination that two small-molecule drugs are the "same" without knowledge of the innovator's manufacturing processes. In other words, the product quality attributes are fully delineated and defined by the drug's "specifications." Therefore, when FDA approves a generic copy of such a drug, it does not require access to the trade secret methods and process data generated by the innovator company.

The same does not hold true for biotechnology-derived products. As the Raptiva® and Eprex® examples show, analytical testing does not always reveal all information critical to assessing how the finished biotechnology-derived product will behave in the human body. Genentech believes that this information is critical to FDA's public health mission. But, under current law, FDA may not use or disclose trade secret data submitted by any applicant without the express permission of that applicant. Section 301(j); 21 CFR 314.50(g)(3). Thus, FDA cannot reference or rely upon trade secret information contained in a Genentech CMC section to approve a section 505(b)(2) application for generic human growth hormone product or to approve a generic

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22/ We note, however, that even with small–molecule drugs significant questions can arise concerning the structure of the molecule. For example, the FDA's 2003 revisions to the rules governing patent listings acknowledges that polymorphs of a crystalline drug may have detectable effects on the bioavailability and bioequivalence of a drug product. 68 FR 36676, 36678-79 (June 18, 2003).

biologic "similar" to a Genentech product approved under section 351 of the PHSA.

e. Nor Can FDA Use Genentech's Confidential Commercial Data and Information to Approve a Product Made From Different Manufacturing Processes

Valuable business data or information that is customarily considered confidential and not disclosed to the public falls within the category of "confidential commercial data and information." *See* 21 CFR 20.61(b). Clinical trial results and certain other information about the use of biotechnology-derived products in patients are considered confidential and are not disclosed by FDA.23/ The agency may release such data and information but only after certain milestone events have occurred, such as eligibility of the product for generic competition under the ANDA provisions of the FDCA. *See* 21 CFR 314.430(e) & (f); section 505(l) of the FDCA, 21 USC 355(l). As a matter of practice, FDA does not release raw data concerning clinical trial results unless extraordinary circumstances exist. *Id.* at 314.430(d).24/

That the proprietary "confidential commercial" data and information under consideration at FDA now has commercial value and is inexorably linked to the manufacturing processes used to create the biotechnology-derived product tested is clear. In 1974, when drafting FOIA regulations, the agency made all safety and effectiveness data contained in BLAs public immediately on approval of the product – in contrast to drug products where such data are not made public until much later. FDA did so because it concluded that data about one unique biological product would never be relevant to a similar

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23/ *See Tri-Bio Labs., Inc. v. United States,* Civil No. 86-0083, FDA's Memorandum in Support of Motion to Dismiss or, In the Alternative, For Summary Judgment 62 (D. Pa. 1986) ("Since 1938, FDA has consistently taken the position that unpublished safety and effectiveness data submitted as part of an . . . NDA are confidential, proprietary information"); *Tri-Bio Labs., Inc. v. United States,* No. 87-5123, FDA's Appellate Brief 43 (3d Cir. 1987) (stating that the FDCA and regulations "recognize that safety and effectiveness data . . . are confidential") (hereafter, "*Tri-Bio Labs.* Appellate Brief"). (The *Tri-Bio* briefs were filed as exhibits to a citizen petition filed by the Biotechnology Industry Organization on April 25, 2003, and are available through FDA's Division of Dockets Management.)

24/ Despite the fact that the plain meaning of the biological product regulations would allow such release, Genentech is not aware of any such release of its safety and effectiveness data or that of any other company. 21 CFR 601.51(e)(1). For example, the agency released only summary data concerning trials conducted on our breast cancer therapy Herceptin® (trastuzamab). Available at http://www.fda.gov/cder/biologics/products/trasgen092598.htm. Although the agency has been required to release raw data in certain limited circumstances, such as after they were provided to advisory committee members, such releases are rare. *See Public Citizen v. FDA & G.D. Searle,* Civil Action 99-0177-JR (D.D.C. 1999).

biological product and would thus have no commercial value to a potential competitor:

> Unlike the regulation of human and animal drugs, all biological products are required to undergo clinical testing in order to demonstrate safety, purity, potency, and effectiveness prior to licensing, regardless whether other versions of the same product are already marketed or standards for the product have been adopted by rulemaking. . . . This is required because all biological products are to some extent different and thus each must be separately proved safe, pure, potent, and effective. . . . [A BLA] is *under no circumstances granted by [FDA] to a second manufacturer based upon published or otherwise publicly available data and information on another manufacturer's version of the same product.* Under section 351 of the [PHSA], biologics never become "old drugs" . . . . Thus, the regulatory scheme for biologics is quite different from the methods by which new drugs and antibiotic drugs are controlled under sections 505 . . . of the [FDCA].

39 FR at 44641 (emphasis added). FDA has never withdrawn this policy statement nor initiated public notice and comment rulemaking to change the FOIA rules. Thus, Genentech and others continue to rely on it when submitting immensely valuable data about biotechnology-derived products to the agency for review and safekeeping – just as we relied on these principles when submitting data and information for complex therapeutic proteins in NDAs.

Genentech does not believe that the agency's interpretation of its authority under section 505(b)(2) applies to the unique legal and scientific issues presented by biotechnology-derived products.25/ Section 505(j) is the only statutory provision that expressly allows confidential commercial data and information contained in a marketing application to be used to approve a competitor's application without the owner's express consent. That section was specifically written by Congress to allow reliance in limited circumstances on confidential commercial data and information – information that is proprietary but about which summaries are made available to physicians and patients in

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25/ Nor does Genentech agree with the agency's legal interpretation of its authority to rely on innovators' data under section 505(b)(2). *See generally* Petition Response. But, we do not repeat those arguments here because they have been vetted in numerous other petitions and repetition would be futile.

labeling. The fact that this information is made publicly available in summary form does not change the fact that it is protected under the law from disclosure by the agency or that it is inexorably linked to the manufacturing processes used to create the biologically active therapeutic protein on which the studies at issue were performed.

Consequently, FDA cannot rely on data obtained by testing a biotechnology-derived product manufactured using one process to approve another biotechnology-derived product manufactured using a different process without first addressing this Federal Register statement and clarifying – in a public process with notice and opportunity for comment – its applicability to all biotechnology-derived products, including those approved under NDAs.

3. UNAUTHORIZED USE OF OUR PROTECTED DATA AND INFORMATION WOULD BE AN UNCONSTITUTIONAL TAKING

The Constitution affords procedural and substantive protection to owners deprived of property by the government. The government cannot take protected private property for public use without providing just compensation and notice and the opportunity to be heard before such a taking. U.S. Constitution, Fifth and Fourteenth Amendments; *Board of Regents v. Roth,* 408 U.S. 564, 569-70 (1972).

a. Use of Genentech's Trade Secret and Confidential Commercial Data and Information by FDA Would Constitute a Taking

To determine whether a taking of property has occurred, courts evaluate three factors: (1) the character of agency action, (2) the economic impact of agency action, and (3) the agency's interference with reasonable investment-backed expectations. *See PruneYard Shopping Center v. Robbins,* 447 U.S. 74, 83 (1980). The last factor is central to the question whether a property interest in trade secrets or confidential commercial data and information is protected. *See, e.g., Monsanto,* 467 U.S. 986; *Tri-Bio Labs., Inc. v. United States,* 836 F.2d 135 (3d Cir. 1988).

An "explicit governmental guarantee" through either a statute or regulation that trade secrets or confidential commercial data and information will not be used by the agency creates a reasonable investment-backed expectation that the trade secret or confidential commercial data and information will be protected under the Fifth Amendment. *Monsanto,* 467 U.S. at 988, 1011. Indeed, in *Tri-Bio Labs*, the court held that an expectation was created through a regulation that requires prior consent before information

contained in one animal drug application may be referenced or relied upon for the consideration of another such application. *Tri-Bio Labs.*, 836 F.2d at 140-41. The same regulation applies to NDAs. *See* 21 CFR 314.50(g)(3).26/

Notwithstanding statutes and regulations, reasonable investment-backed expectations can also be created from "understandings that stem from an independent source."27/ The threshold question is whether there is more than a "unilateral expectation or an abstract need."28/ FDA's long practice of protecting both trade secret and confidential commercial data and information has established such a claim by Genentech. *See* 21 CFR Part 20; 21 CFR 314.430; FDA *Acceptance of Commission Oath*; August 1996 Zonana letter, at 3. And, the First Circuit recently recognized that ingredient information is trade secret data that cannot be taken even in a quest to improve the public health. *See Reilly*, 312 F.3d at 38-39, 45-46. Information about cell cultures, fermentation media, process impurities, and the like similarly are ingredient information that cannot be used or released by FDA – despite the merits of the agency's public policy goals.

b. Genentech Is Entitled To Notice, Hearing, And An Opportunity For Judicial Review Before FDA Issues A Guidance Document Or Approves A Generic Copy Of Any Genentech Biotechnology-Derived Product Based on Genentech's Protected Data and Information.

Administrative agencies must provide notice, a hearing, and an opportunity for judicial review before releasing trade secret data. *American Sumatra Tobacco Corp. v. SEC*, 93 F.2d 236, 239 (D.C. Cir. 1937). And, FDA provides an elaborate process under which it will provide to NDA applicants an opportunity to review records and seek judicial review before the agency will

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26/ In the Petition Response, the FDA stated that pharmaceutical companies could not reasonably expect that the FDA would not make "changes in the regulatory scheme" that would affect the value of their investments. Petition Response at 31. Not only is this an unusually novel interpretation of Supreme Court precedent, it fails to even acknowledge the agency's own previous position that the FDA could not rely on confidential commercial data and information of one sponsor to approve another sponsor's product. *See Tri-Bio Labs.* Appellate Brief, at 39, 43-44.

27/ *Monsanto*, 467 U.S. at 1001 (quoting *Roth*, 408 U.S. at 577).

28/ *Id.* at 1005 (quoting *Webb's Fabulous Pharmacies, Inc. v. Beckwith*, 449 U.S. 155, 161 (1980); *see also Perry v. Sindermann*, 408 U.S. 593, 602 (1972) ("unwritten 'common law'" may create a property interest); *see also Orloff v. Cleland*, 708 F.2d 372, 377 (9th Cir. 1983) ("Despite the apparent expiration date of [plaintiff's employment] contract there may have arisen an understanding of continued employment based on prior treatment . . . sufficient to constitute a *de facto* property interest").

release records under the FOIA. 21 CFR 20.61; Executive Order 12600 (June 23, 1987). Indeed, FDA acknowledged these procedural rights when it promulgated the FOIA regulation. 39 FR at 44614, cmt. 96. Should it fail to provide these procedural protections, release of any data would not be "authorized by law" – subjecting the agency to a potential injunction. *Chrysler v. Brown*, 441 U.S. 281. The same principles apply with equal force here – where FDA relies on protected information to publish a draft guidance or review and approve another company's application, the agency must first establish procedures to protect the owner of the data and information. .

Despite these obligations, FDA is apparently reviewing at least one application submitted under section 505(b)(2) that will, at least in part, rely on Genentech's protected data and information. Under the agency's current practice, the only parties that may participate in that secret process are the agency and Genentech's potential competitor – we are prohibited from even receiving information about the process, much less from participating in it. This secret process flies in the face of the constitutional principles that FDA has otherwise recognized – when our trade secrets and confidential commercial data and information are at issue, Genentech has the right to notice, a hearing, and the opportunity to seek judicial review – before any such use or disclosure occurs.29/ The agency should stop any such review now and put in place procedures that will allow Genentech and other innovators to participate in those processes where trade secret and confidential commercial data and information may be used for the benefit of someone other than the owner of those data.

C. CONCLUSION

FDA must not take steps to publish a draft guidance concerning the concept of "similarity" between two biotechnology-derived products without first meeting its statutory obligations to protect trade secret and confidential commercial data and information entrusted to it for very limited purposes – assuring the safety and effectiveness of innovator products. Because trade secret rights and rights in confidential commercial data and information can be

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29 / When an application is under review for approval, we do not believe that the FDA can legitimately distinguish between use and disclosure of trade secret or confidential commercial information. The agency is statutorily prohibited from using our data to benefit another person. Section 301(j). Similarly, any prohibition on disclosure exists for the same reason – to prevent a competitor from obtaining our data from the FDA and using it to our competitive disadvantage. *See* 39 FR at 44641. Thus, there is no practical difference between use and disclosure of Genentech's protected data.

destroyed by any public disclosure, FDA must refrain from disclosing – directly or indirectly – Genentech information that has been entrusted to it.

And, FDA must also refrain from approving any biological product based on Genentech's proprietary safety and effectiveness data and information or a comparison with a Genentech product until FDA has established an administrative process to protect our trade secret and confidential commercial data and information. The sensitivity associated with the use of trade secret and confidential commercial data and information warrants the highest sensitivity to this task by the agency. As the actions surrounding the Dr. Reddy's amlodipine approval demonstrate, agency review staff may be confused about what materials may be reviewed during the consideration of an application submitted under section 505(b)(2). Genentech has no reason to believe that the standard is any clearer with respect to any other type of application – especially one pertaining to a biotechnology-derived product where the inseparability of product and process is a scientific certainty. Therefore, we urge the agency to adopt – at a minimum – a process that will provide notice, a hearing, and a meaningful opportunity to object before Genentech's property is used to approve a competitor's product.

D. ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusions under 21 CFR 25.30 and 25.31.

E. ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted upon request of the Commissioner of Food and Drugs.

F. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Respectfully submitted,

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Counsel, and Secretary

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Hogan & Hartson, L.L.P.